Effect of Crystallinity of Microcrystalline Cellulose on Granulation in High-shear Mixer[1)]

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Granulation was carried out using binary mixtures of microcrystalline cellulose (MCC) and cornstarch (CS); water was used as granulating liquid. The effect of crystallinity of MCC on granulation was examined using MCC pulverized by a jet mill (J-MCC) and a vibrational rod mill (R-MCC). Crystallinity of J-MCC was nearly equal to that of intact MCC (I-MCC), but that of R-MCC was remarkably low due to the mechanochemical effect. The growth rate of granules with R-MCC was greater than those with I-MCC and J-MCC; the latter two had a grnule having a core (MCC and CS) around which CS was layered. R-MCC provided granules in which CS and abraded MCC were homogeneously mixed. In addition, R-MCC remarkably decreased the difference in drug content among the size fractions of granules compared with I-MCC. These results suggest that the decrease in crystallinity of MCC may increase the tendency of its abrasion by shear force of impeller, because of an increase of the fragile amorphous region swollen by added water; this, in turn, results in a difference in the growth mechanism and in a greater growth rate.

Keywords microcrystalline cellulose; crystallinity; granulation; high-shear mixer

High-shear mixers have been widely used for the wet granulation of drugs. With such mixers, mixing, densification and agglomeration of wetted materials can be quickly achieved as a result of the high shear force of the impeller, which rotates at a high speed.

Studies relating operation factors have been reported. Holm *et al.* reported the effect of operation factors such as impeller speed, liquid flow rate, chopper speed and so on.[3)] Carstensen *et al.* reported that the strength of granules was increased when the distribution of water as granulating liquid was improved.[4)] For automation of the process, methods for determining granulation end point have been reported. Leuenberger *et al.* investigated the power consumption of the rotating impeller in the granulating process,[5,6)] while Cliff measured the torque of the main impeller.[7)]

It is important for particulate design and product preparation to understand the behavior of each additive in the granulation process. Lactose and calcium phosphate were often used as a typical water soluble material and a water insoluble material, respectively,[3,8)] and the effect of characteristics of these materials on granulation was examined. Microcrystalline cellulose (MCC) is also one of the most popular excipients used for granulation in a high-shear mixer. However, it is not yet clear how MCC behaves in the granulation process.

In this study, the effect of crystallinity of MCC on granulation was examined using MCC pulverized by a jet mill (J-MCC) and a vibrational rod mill (R-MCC).

Experimental

Materials and Method The materials used were MCC (Avicel PH-101, Asahi Chemical Industry Co., Ltd., Japan), cornstarch (CS, XX16-W, Nihon Syokuhin Kako Co., Ltd., Japan), lactose (Pharmatose, DMV, the Netherlands), ethenzamide (Shizuoka Caffeine Industry Co., Ltd., Japan) as a drug with low solubility and ascorbic acid (Daiichi Pharmaceutical Co., Ltd., Japan) as a drug with high solubility of J.P. XII grade. Both ethenzamide and ascorbic acid were passed through a 75 μm sieve before use. Their powder characteristics are shown in Table I. Water was used as the granulating liquid in order to keep the granule composition simple.

Intact MCC (I-MCC) was finely pulverized by a jet mill (PJM-NP, Nihon Pneumatic Co., Ltd., Japan) under the following conditions: compressed air consumption, 2.0 kg/nm^3/min; air pressure, 6.5 kg/cm^2; sample feed, 0.5 kg/h and a vibrational rod mill (Sample Mill, Heiko Co., Ltd., Japan) in which the sample amount was 3 g and grinding time was 10 min. The abbreviations used are: I-MCC, intact MCC; J-MCC, MCC ground by a jet mill; R-MCC, MCC ground by a vibrational rod mill.

Granulation Method The granulation was carried out by an FS-5 high-shear mixer (Fukae Powtec, Japan) which is equipped with a 3-blade main impeller, but has neither a chopper nor a cooling jacket. Rotating speed of the impeller was kept at 640 rpm. The batch scale of granulation was about 1 kg, and water used as the granulating liquid was poured in all at once. Samples were taken at 3, 6, 9, 12 and 15 min after the water addition. The damp mass sampled was dried in a tray dryer at 40 °C for 5 h.

Granulation Using Various MCC The effects of the differences in characteristics of the MCC (I-MCC, J-MCC and R-MCC) on the granulation mechanism were examined using binary mixtures with an MCC/CS ratio of 200/600. Granulation was carried out by mixing MCC and CS at the same time, and then kneading them as water was added.

We also examined the difference in drug content among the size fractions of granules prepared using the formulation given in Table II.

TABLE I. Powder Characteristics

Powder	Mean particle size (μm)	Bulk density (g/cm^3)
MCC	50	0.29
CS	20	0.49
Lactose	40	0.58
Ethenzamide	55	0.29
Ascorbic acid	60	0.53

TABLE II. Formulation of Granules

MCC	200 g
CS	600 g
Lactose	100 g
Ethenzamide or ascorbic acid	100 g

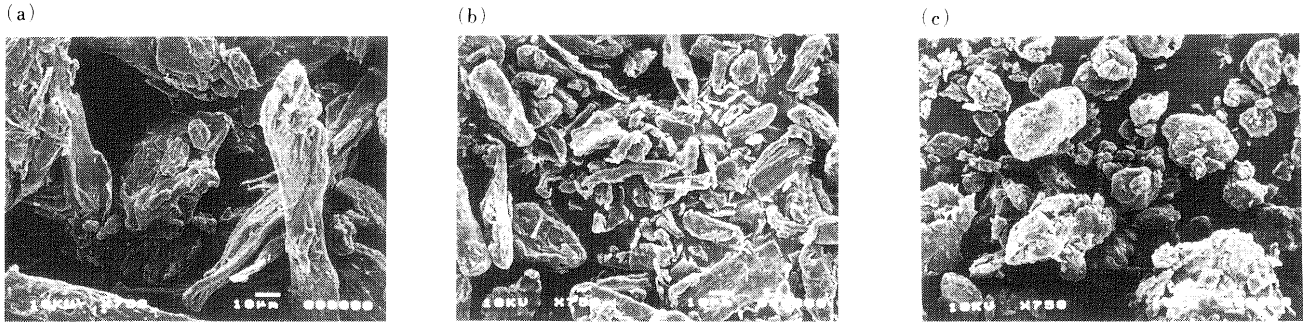

Fig. 1. Scanning Electron Micrographs of Various MCC
(a) I-MCC, intact MCC; (b) J-MCC, MCC ground by a jet mill; (c) R-MCC, MCC ground by a vibrational rod mill.

Granulation with Different Addition Order of I-MCC The granulation was carried out using a binary mixture of I-MCC and CS at a ratio of 200 : 600. Three different procedures were followed:

Method A: I-MCC alone was kneaded with water for 1 min, then CS was added, and further kneading was carried out.

Method B: The two components were mixed at the same time, and then kneaded with the addition of water.

Method C: CS alone was kneaded with water for 1 min, then I-MCC was added, and further kneading was carired out.

The growth rates following these procedures were compared by measuring mean granule size.

Measurement The particle size of each material was measured by a particle size analyzer using a laser beam (Microtrac II, Leeds & Northrup Co., Ltd., U.S.A.).

The granule size distribution was measured by sieve analysis, and the mean granule diameter was calculated by the regression lines of cumulative weight percentages of sieved fractions to log-normal distribution.

Power X-ray diffraction was carired out using a diffractometer (MPX^3, Mac Science, Japan) with Ni-filtered, Cu-$K\alpha$, radiation. The crystallinity of MCC was calculated by Hermans' method.

Scanning electron micrographs (SEM) were taken with a JSM-T220A microscope (JEOL, Japan).

The ethenzamide and ascorbic acid in the granules were assayed by UV spectrophotometry and by the iodine titration method, respectively.

Results and Discussion

Crystallinity of MCC and Mechanism of Granulation Figure 1 shows SEM of each MCC.

I-MCC particles were fibrous, while J-MCC particles were smaller than I-MCC but still showed a fiber-like shape. In contrast, R-MCC particles were almost round in shape.

The mean particle diameters and porosities of the MCC used are listed in Table III.

Figure 2 shows the powder X-ray diffraction patterns of the MCC used.

With R-MCC, the sharp diffraction peaks attributed to the crystal region of MCC decreased, and its crystallinity was markedly reduced from 65% to 23%, owing to the mechanochemical effect. The mean particle diameter of J-MCC was considerably less, but its crystallinity was almost the same as that of I-MCC.

The mean diameters of granules prepared using MCC with different crystallinities are shown in Fig. 3.

The growth rate of granules with R-MCC was greater than that with J-MCC or I-MCC. R-MCC in which a large proportion is amorphous may possibly absorb much more water than I-MCC or J-MCC, thus promoting granule growth.

TABLE III. Characteristics of MCC Used

MCC	Mean diameter (μm)	Porosity	
		Poured	Tapped
I-MCC[a]	50	0.83	0.74
J-MCC[b]	16	0.86	0.76
R-MCC[c]	42	0.78	0.61

a) Intact MCC. *b*) MCC ground by a jet mill. *c*) MCC ground by a vibrational rod mill.

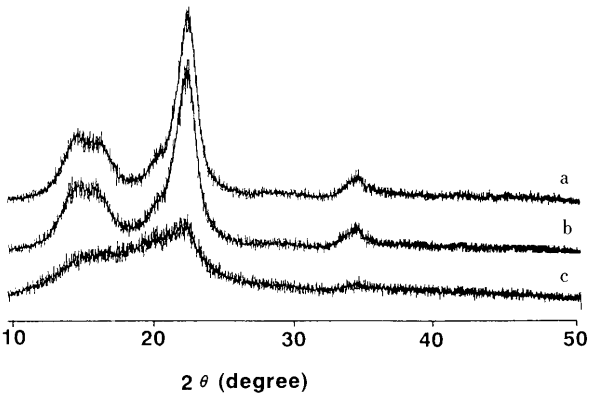

Fig. 2. Powder X-Ray Diffraction Patterns of Various MCC
(a) I-MCC, intact MCC (crystallinity: 65%); (b) J-MCC, MCC ground by a jet mill (crystallinity: 63%); (c) R-MCC, MCC ground by a vibrational rod mill (crystallinity: 23%).

To determine the effect of water distribution between MCC and CS on the growth rate, granulation was carried out with different addition order of I-MCC.

The mean granule diameters resulting from the three methods differed, as shown in Fig. 4.

The growth rates of granules were decreased in the order, method A, method B, method C, and the amounts of water absorbed into I-MCC might have decreased in the same order. In method A, I-MCC might be able to absorb much more water than CS; in method B, I-MCC and CS competed for the water; and in method C, CS might be able to absorb much more water than I-MCC. It is therefore presumed that I-MCC becomes swollen as a result of large water intake into the polymer chains, consequently promoting the growth rate.

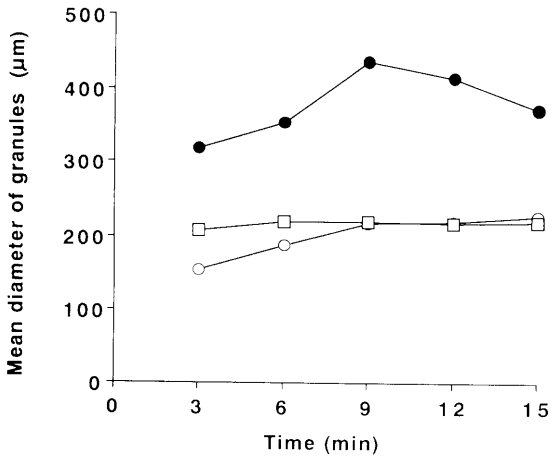

Fig. 3. Changes in the Mean Diameter of Granules during the Granulation Process

○, I-MCC, intact MCC; □, J-MCC, MCC ground by a jet mill; ●, R-MCC, MCC ground by a vibrational rod mill.

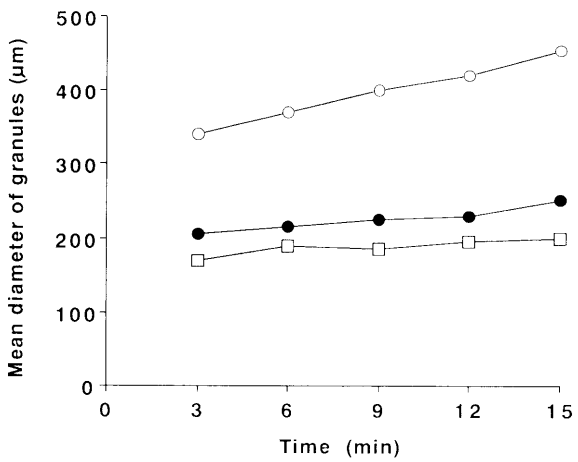

Fig. 4. Changes in the Mean Diameter of Granules during the Granulation Process

○, method A, I-MCC alone was kneaded with water, and then CS was added; ●, method B, both I-MCC and CS were kneaded with water at the same time; □ method C, CS alone was kneaded with water, and then I-MCC was added.

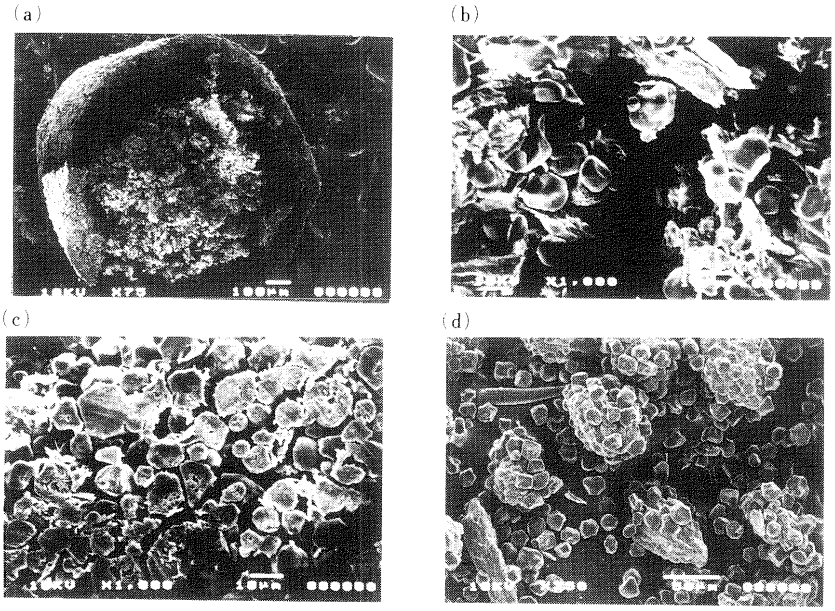

Fig. 5. Scanning Electron Micrographs of I-MCC/CS Granules

(a) Granule (850–1400 μm fraction); (b) core particle of granule (850—1400 μm fraction); (c) outer layer of granule (850—1400 μm fraction); (d) granules (≤75 μm fraction).

Figure 5 shows a cross-section of a granule with I-MCC; a core particle and the outer layer surrounding the core particle were observed in the large-size fraction (850—1400 μm, Fig. 5a). The core particles were constituted of CS particles bridged by I-MCC (Fig. 5b), while the outer layer consisted of CS particles alone (Fig. 5c). Many ungranulated CS particles were also observed in the small-size fraction (≤75 μm, Fig. 5d), and the SEM of J-MCC granules were similar to those of I-MCC.

For granules prepared using R-MCC, however, a homogeneous structure was observed in the large-size fraction (850—1400 μm, Fig. 6a). Moreover, scarcely any ungranulated CS particles were observed in the small-size fraction (≤75 μm, Fig. 6b).

SEM suggested that the methanism of granulation using I-MCC and J-MCC is different from that using R-MCC. Figure 7 shows proposed mechanisms for granulation using different types of MCC. For I-MCC and J-MCC, the crystal region occupies a high proportion of the MCC fiber structure. The crystal region may be hard because of its rigid structure, and may not be able to uptake much water into its polymer chain. It is therefore considered I-MCC and J-MCC cannot be broken up by an impeller to a sufficient extent to bridge all existing CS particles together. CS particles which could not be bridged may form a layer on the surface of the core granules, resulting in granules with a two-layer structure (Fig. 7a). R-MCC has a large and fragile amorphous portion in its structure, and this portion was believed to be swollen by water and easily broken up by the impeller, causing a size

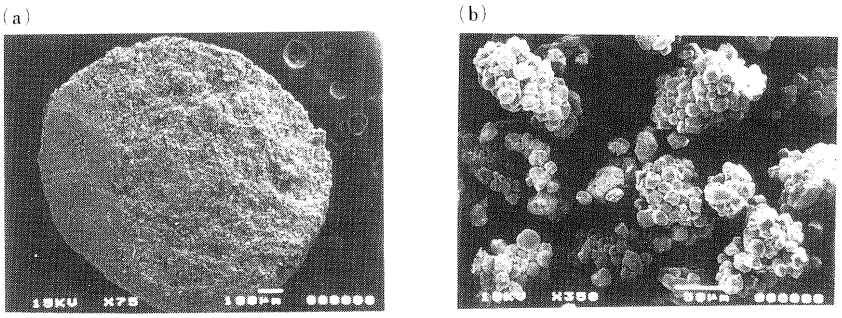

Fig. 6. Scanning Electron Micrographs of R-MCC/CS Granules
(a) Granule (850 1400 μm fraction); (b) granules ($\leq$75 μm fraction).

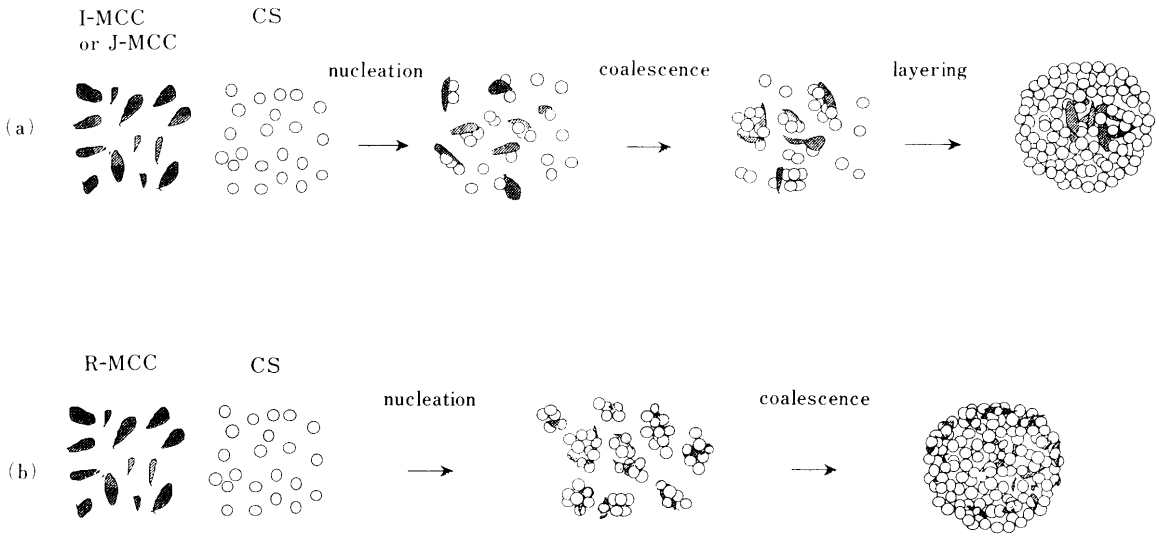

Fig. 7. Proposed Mechanisms for Granulation of MCC and CS in a High-shear Mixer
(a) Granulation mechanism for MCC with high degree of crystallinity; (b) granulation mechanism for MCC with low degree of crystallinity.

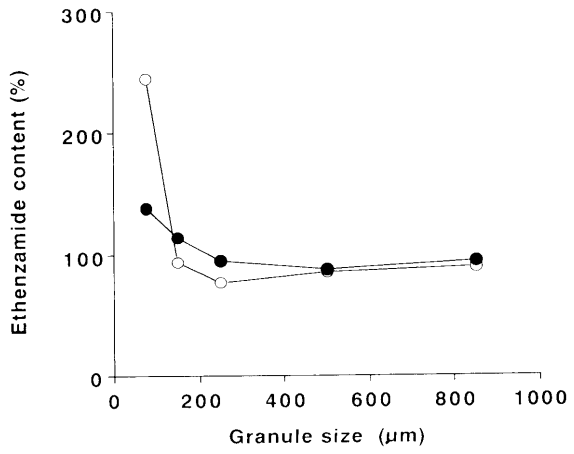

Fig. 8. Ethenzamide Content of Each Granular Fractions
○, I-MCC, intact MCC; ●, R-MCC, MCC ground by a vibrational rod mill.

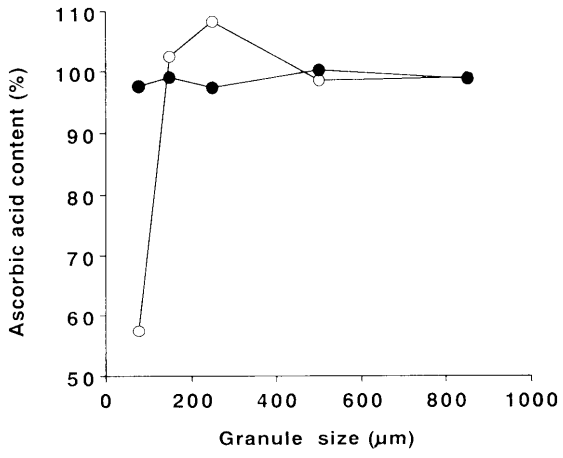

Fig. 9. Ascorbic Acid Content of Each Granular Fractions
○, I-MCC, intact MCC; ●, R-MCC, MCC ground by a vibrational rod mill.

reduction in the granulation process, as suggested in a previous paper.[9] Hence, R-MCC can bridge the CS particles homogeneously, and layering with CS particles cannot occur (Fig. 7b).

Effect of Crystallinity of MCC on Difference in Drug Content Among the Size Fractions of Granules We examined the relationship between difference in drug content among the size fractions of granules and the mechanism of granulation. The granulation was carried out using I-MCC and R-MCC, and ethenzamide and ascorbic acid were used as model drugs.

Figures 8 and 9 show the difference in ethenzamide content and ascorbic acid content of granules, respectively, among the size fractions. For granules prepared using

I-MCC, the contents of ethenzamide and ascorbic acid were higher and lower, respectively, in the small-size fraction ($\leq 75\,\mu m$). In the ethenzamide granulation, ethenzamide remained ungranulated in the small-size fraction because it has poor wettability, so that we recognized a higher content of the drug in this fraction. In the ascorbic acid granulation, ascorbic acid is an advantageous component for granulation in the formulation, because it exhibits good wettability. In this granulation, ungranulated lactose particles remained in the small-size fraction, so lower ascorbic acid content was recognized in this fraction.

For granules prepared using R-MCC, the difference in drug content among the size fractions were greatly decreased in comparison with granules prepared using I-MCC, because R-MCC could homogeneously bridge the other components in the granulation process.

In this way, the difference of the mechanism of granulation affects the difference in drug content among the size fractions of granules.

Conclusions

The crystallinity of R-MCC was reduced compared with those of I-MCC and J-MCC, owing to the mechanochemical effect. The growth rate of granules with R-MCC was greater than those with I-MCC and J-MCC, and the structure of a granule prepared using R-MCC differed from those of granules prepared by the other two means. The granule with I-MCC and J-MCC had a core particle (MCC and CS) and an outer layer (CS) surrounding the core particle, while the granule with R-MCC exhibited a structure in which abraded MCC and CS were homogeneously mixed. Moreover, R-MCC decreased the difference in drug content among the size fractions of granules more than I-MCC.

The growth rate is probably increased by an increase in the amount of water taken up by the MCC particles. R-MCC may absorb much more water than I-MCC or J-MCC because of its fragile amorphous structure, resulting in a greater growth rate.

Differences in the degree of crystallinity of MCC are closely related to the capacity for bridge formation, and result in different mechanisms of granulation. MCC in which a large proportion is amorphous can easily be broken up by the force of impeller, and can bond other homogeneous particles together. In contrast, MCC in which a large proportion is crystalline may be more resistant to being broken up by the impeller, so that many other ungranulated particles may remain in the small-size fraction. These ungranulated particles may deposit on the external surface of the granules during the layering process.

It has been shown that the difference in drug content among the size fractions is decreased when MCC with low degree of crystallinity is used as an excipient in granulation.

The possible bridge formation of MCC was suggested only by SEM, so further study is required to clarify this formation.

References and Notes

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